IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDPOINTE HEALTHCARE INC.,	)	
	)	
Plaintiff,	)	C.A. No. 06-164 (SLR)
	)	
v.	)	
	)	
APOTEX INC. and APOTEX CORP.,	)	
	)	
Defendants.	)	

DEFENDANTS' INITIAL CLAIM CONSTRUCTION BRIEF

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INTRODUCTION AND SUMMARY

In 1992, U.S. Patent No. 5,164,194, entitled "Azelastine Containing Medicaments" (hereinafter sometimes referred to as "the '194 patent") issued to Hettche. (Exhibit A, attached hereto, and filed previously as Exhibit A to the Amended Complaint, D.I. 5). This is despite azelastine and its topical administration to treat allergic conditions both being known and described in the prior art. However, to escape invalidating prior art, MedPointe is attempting to drastically (and impermissibly) narrow the scope of the claims at issue. MedPointe specifically seeks to re-define simple English phrases and known medical terms — "irritation or disorder", "nose and eye", "medicament" and others — as if these terms were coined by the inventors and/or used in ways that are so inconsistent with their ordinary meanings that the inventors implicitly re-defined the terms. MedPointe similarly seeks impermissibly to manufacture new claim limitations from FDA approval requirements and litigation-inspired arguments extolling their commercial product's virtues, *e.g.*, that "medicament" be re-defined as something that is necessarily safe, effective, and tolerable for use in humans — despite the absence of these words from the patent claims and, generally, from the patent specification.

NATURE AND STAGE OF PROCEEDINGS

This is a patent case brought under 35 U.S.C. § 271(e), part of the Hatch-Waxman act concerning brand-name and generic pharmaceuticals. The case is scheduled for a bench trial in February 2008 on issues including non-infringement, invalidity, and unenforceability for inequitable conduct and/or fraud on the patent office in procuring the patent. A critical step in any patent case is claim construction, the interpretation of patent claim language, as explained in more detail in the balance of this brief. This brief sets forth defendant Aptoex's position regarding the proper construction of disputed claim language.

SUMMARY OF THE ARGUMENT

All the claim terms should be given, in the first instance, their ordinary and accustomed meaning. The plaintiff patentee MedPointe in this case in general seeks to import additional limitations into the claim, based on concepts such as efficacy, safety, and tolerability. Although those concepts are relevant to commercial pharmaceutical products in general, they were ***not*** the basis for the issuance of this patent and should not be considered limitations of these claims, which do not recite such language.

ARGUMENT

I. Claim Construction and Federal Circuit Precedent

Claims must be construed before determining whether they are valid or infringed and must be construed the same way for determining validity and infringement. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976, 996 n. 7 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996).

Claim construction is a question of law to be addressed in the first instance by the District Court, wherein the scope of the claimed invention is determined as would be understood by a person having ordinary skill in the art. *Markman*, 52 F. 3d at 970-71; *Schoell v. Regal Marine Indus., Inc.*, 247 F.3d 1202, 1207 (Fed. Cir. 2001); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (*en banc*).

A. The Claims, Not Examples or Arguments, Define The Invention.

The public notice demanded by the patent statute has the effect of requiring that claim language be interpreted based upon what it actually says, not what one suspects the inventor might have meant or could have written. In particular, limitations cannot be imported into the claims from the specification. As the Supreme Court long ago explained:

> [W]e know of no principle of law which would authorize us to read into a claim an element which is not present, for the purpose of making out a case of novelty or infringement. The difficulty is that if we once begin to include elements not mentioned in the claim in order to limit such claim and avoid a defence [sic] of anticipation, we should never know where to stop.

McCarty v. Lehigh Valley R. Co., 160 U.S. 110, 116 (1895); *accord*, *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433–34 (Fed. Cir. 1988). The court in *E.I. du Pont de Nemours* held that the district court erred in interpreting the claims as including properties of "environmental stress crack resistance" and "impact strength", which the district court believed to be "the essence" of the invention. 849 F.2d at 1432–33.

B. The Court Looks First To The Plain Meaning Of The Terms.

Proper claim interpretation looks to the entire patent document from the point of view of one having skill in the art with which the patent is concerned. *Philips v. AWH Corp.*, 415 F.3d 1303, 1313-1316 (Fed. Cir. 2005) (*en banc*). Claim terms are generally accorded their ordinary and customary meaning as would be understood by that person as of the effective filing date of the patent application when read in the context of the entire patent. *Id.* at 1314.

C. Intrinsic Evidence In The Claims, Specification And File History Is The Primary Sources For Interpretation.

In determining the meaning of disputed claim language, a court looks first to the intrinsic evidence of record, examining, in order, the claim language itself, the specification, and the prosecution history. *Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1370 (Fed. Cir. 2004). The meaning of claim terms will typically be found in the specification (which includes the claims) because a patent specification must satisfy the statutory requirement that the patent clearly describe the claimed subject matter. *Philips*, 415 F.3d at 1315. Where the patent gives a specific definition of a claim term, "the inventor's lexicography governs," even if the definition is at odds with the usual understanding of such term. *Id* at 1316. "[T]he specification is always highly

relevant to the claim construction analysis," and "[u]sually, it is dispositive." *Id.* at 1315. Where doubts remain or technical terms remain unclear, it can be useful to consult the prosecution history, and perhaps other sources such as dictionaries. *Id* at 1317-18.

The prosecution history of the patent provides the next resource for construing the claims because it "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Philips* at 1317. "The prosecution history constitutes a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to rely on those representations . . . ." *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000). Nevertheless, "[u]nless the intrinsic evidence compels a contrary conclusion, the claim language carries the meaning accorded those words in the usage of skilled artisans at the time of invention." *Smithkline-Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1338-39 (Fed. Cir. 2005) (emphasis added).

D. The Court Can Also Consider Extrinsic Evidence In Some Circumstances, But Not To Alter The Meaning Imparted By The Intrinsic Record

Under certain circumstances, "extrinsic evidence [such as dictionaries, learned treatises, and testimony] concerning relevant scientific principles, the meaning of technical terms, and the state of the art" may be useful in interpreting the claims, *Philips* at 1314, but "is less reliable than the patent and its prosecution history in determining how to read claim terms." *Id.* at 1318. In particular, such evidence will not be allowed to "contradict any definition found in or ascertained by a reading of the patent documents." *Id.* at 1322-23.

To ascertain the plain and ordinary meaning of technical terms inadequately defined in the patent and the patent file history, the court can consider extrinsic evidence, such as expert

testimony. *See e.g.*, *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1122 (Fed. Cir 2004); *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1300 (Fed. Cir. 2003). *See also*, *Tex. Digital Sys. Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1203 (Fed. Cir. 2002). However, expert testimony regarding claim interpretation is only to be considered

> "if the patent documents, taken as a whole, are insufficient to enable the court to construe disputed claim terms. ***Such instances will rarely, if ever, occur.*** . . . Even in those rare instances, prior art documents and dictionaries, although to a lesser extent, are more objective and reliable guides. . . . Indeed, opinion testimony on claim construction should be treated with the utmost caution, for it is ***no better than opinion testimony on the meaning of statutory terms***."

Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1585 (Fed. Cir. 1996) (emphasis added), citing *Markman*, 52 F.3d at 970–71; *accord.*, *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298 (Fed. Cir. 1999).

II. Apotex's Proposed Claim Construction

It is Apotex's position that the overwhelming majority of the terms of the '194 patent should be construed to have their plain and customary meaning. Furthermore, the '194 patent claims should be accorded their full and natural scope as would have been apparent to skilled artisans at the time of the invention, and not limited by litigation-inspired *ex post* considerations. Accordingly, the following discussion will highlight the full scope of what the claims plainly require, as well as limitations *not* found in the claims but asserted by MedPointe. (*See*, Joint Claim Construction, D.I. 101.)

A. The Plain And Ordinary Meaning Of "Irritation Or Disorders Of The Nose And Eye"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"irritation or disorders of the nose and eye"	Rhinitis and/or conjunctivitis, including seasonal allergic rhinitis and vasomotor rhinitis. Symptoms of rhinitis include itching (also known as "pruritus"), sneezing, increased secretions (also known as "rhinorrea"), and congestion.	Including but not limited to rhinitis and/or conjunctivitis, including seasonal allergic rhinitis and vasomotor rhinitis.

Apotex contends that this recitation need not be interpreted as a limitation of claim 1 and its dependent claims because it is a part of the preamble of claim 1. Preambles to claims are non-limiting where the body of the claim sets out the complete invention, where all the steps and materials necessary to perform the claimed method are provided in the body of the claim. *See e.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1373-4 (Fed. Cir. 2001) (preamble recitations of therapeutic objectives not limiting, discussed further *infra*); *c.f.*, *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339-40 (Fed. Cir. 2003) (where the preamble provided necessary antecedent basis for structures in the body of the claim or necessary structures absent from the body of the claim, the preamble was limiting); *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329 (Fed. Cir. 2003) (the specific condition to be treated so limited the claim because it was added to the preamble by amendment specifically to overcome prior art after 20 years of unsuccessful prosecution). Here, like in *Bristol-Myers*, the preamble at most sets out desired objectives and results of the claimed method, was not added by amendment to overcome prior art, and does not enumerate necessary steps, structures or antecedents.

Furthermore, Apotex contends that if MedPointe wishes the preamble to be limiting in any sense, it is subject to the usual methodology of claim construction. Apotex contends that the meaning of "irritation or disorders of the nose and eye" must, based upon the specification, denote ***at least*** all the disorders and symptoms enumerated in the patent that effect the nose and eye. The inventor explained quite clearly that the method was intended to treat "not only allergy-related rhinitis but also the normal common cold (caused, for example, by rhino viruses) . . . the vasomotor cold and the symptoms of illness triggered thereby," (Ex., A, the '194 patent, col. 1:40-43), as well as "[o]ther indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza." (Ex. A, '194 patent, col. 1:49-52.) To the extent that the preamble here needs construction, Apotex contends that the claim language and specification expressly require that the universe of "irritation or disorders of the nose and eye" include these conditions and more, including diseases and symptoms having infectious, allergic, and non-specific etiologies.

B. The Plain And Ordinary Meaning Of "Applying Directly To Nasal Tissues Or To The Conjunctival Sac Of The Eyes"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"applying directly to nasal tissues or to the conjunctival sac of the eyes"	Topical application to the nose or to the conjunctival sac of the eyes. Excludes oral and parenteral applications.	Ordinary meaning, including but not limited to application directly to mucous membranes of the nose and eye.

Apotex contends that *"applying directly to nasal tissues or to the conjunctival sac of the eyes"* should be construed to have its ordinary and customary meaning, and includes but is not limited to application directly to mucous membranes of the nose and eye. The issue of whether a

particular accused infringing use or a particular prior art reference meets the limitation of "applying directly" poses a question of fact. It would be inappropriate to resolve such factual questions involving comparison of the claim to accused infringements and/or to prior art by a purported "claim construction" that does not say what the claim terminology is, but instead what it is not.

C. The Plain And Ordinary Meaning Of "Azelastine And Its Physiologically Acceptable Salts"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"azelastine and its physiologically acceptable salts"	Azelastine and salts of azelastine that are physiologically safe, effective, and tolerable, such as azelastine hydrochloride.	A salt form of azelastine capable of being administered to an animal via at least one route of administration, including but not limited to the hydrochloride salt of azelastine.

Apotex proposes that "azelastine and its physiologically acceptable salts" be given its ordinary meaning, namely azelastine base and salt forms of azelastine capable of being administered to an animal by at least one route of administration. Physiologically acceptable salts of azelastine include but are not limited to the hydrochloride salt of azelastine.

Salts are compounds that are usually the product of a reaction between an acid and a base, and most drug compounds are sold as salts. The term "physiologically acceptable salts" was used but not discussed during the patent prosecution. The '194 patent specification discusses azelastine salts. (Ex. A, the '194 patent, col. 3:48–55.) There are numerous salts expressly identified in the '194 patent and therefore fall within the scope of the term "physiologically acceptable salts" of azelastine. In the '194 patent, salts useful for the claimed method are enumerated as the acid that is reacted with azelastine base:

> Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

Id. The enumeration of these salts shows that the inventor expressly meant that "physiologically acceptable salts" of azelastine include at least all of these. Of course, there is no indication that, for example, azelastine camphorsulfonate, is safe, effective or tolerable when applied directly to nasal tissues or to the conjunctival sac of the eye, as there is no evidence that these compounds were ever applied to any eyes or nasal tissues of any animal. For this reason alone, MedPointe's proposed interpretation to require safety, efficacy and tolerability should be disregarded.

"Physiologically acceptable" is, however, used in the '194 patent specification in another specific context: "physiologically acceptable solvents". (Ex. A, the '194 patent, col. 2:41.) The "physiologically acceptable solvents (for example those mentioned above)" plainly refers to the immediately preceding discussion of preferred solvents including "saturated aliphatic mono and polyvalent alcohols" such as ethanol (grain alcohol), isopropanol (rubbing alcohol), propylene glycol, glycerine, and liquid polyglycols. (Ex. A, the '194 patent, 2:35–39.) There is no demonstration or suggestion that, for example, a medicament where the "physiologically acceptable solvent" is isopropanol might be safe or tolerable in the usual sense when applied directly to nasal tissues or the conjunctival sac of the eye. Furthermore, common sense suggests that a medicament where alcohol was the solvent would be neither safe nor tolerable when applied directly to either the eye or nose, but might nevertheless be relatively safe and/or tolerable when applied to the skin or taken orally as *e.g.*, a component of an elixir. This shows that "physiologically acceptable" does *not* denote, as suggested by MedPointe, that the salt of azelastine contemplated by the inventor is necessarily "physiologically safe, effective, and

tolerable[1]" for direct application to the nasal tissues and/or the conjunctival sac of the eye. Accordingly, Apotex contends that "physiologically acceptable salt" merely means that the salt be acceptable for *any* manner of administration to an animal — such as oral or topical administration — because the claims, the specification, and the file history support no more limited reading of the phrase.

Claims drawn to pharmaceutical compositions and methods of use are interpreted the same way as any other claims, just as the standards for patentability are the same for all inventions. It is apparent that MedPointe nevertheless wishes this Court to conflate requirements for approval of a drug product by the FDA[2] into the claim construction analysis by interpreting "physiologically acceptable" to mean "safe, effective, and tolerable". *Philips* and other binding precedent prevent just this sort of analytical contamination by requiring that claim interpretation follow a particular path emphasizing the patent and the file history. MedPointe's proposed construction conflicts with Federal Circuit cases even where the patentee expressly recited specific aspects of safety and effectiveness in claims relating to methods of using a pharmaceutical product. In *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001), two claims at issue recited:

> 1. A method for reducing hematologic toxicity in a cancer patient undergoing taxol treatment comprising parenterally administering to said patient an

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[1] Apotex notes that these terms are absent from the specification. "Safe" (either the word the concept) is neither used nor discussed anywhere in the '194 patent or its prosecution. There is no discussion of whether azelastine is safe or unsafe, nor any expression of what "safe" means here: Non-addictive? Non-irritating? Non-corrosive? Non-carcinogenic? Non-sedating? Nor are the words "effective" or "tolerable" used or the concepts concretely addressed anywhere in the '194 patent. The closest is the statement that "the object of the invention is to provide a well-tolerated remedy…", which appears to relate solely to the bitter taste. (Ex. A, the '194 patent, col. 2:3–4. One can only wonder: how safe? How effective? How tolerable?)

[2] 21 U.S.C. § 355(S)(1) (A) requires that the FDA ensure that approved drugs be "safe for [and] effective in use."

> antineoplastically effective amount of about 135-175 mg/m^2 taxol over a period of about three hours.
>
> * * *
>
> 5. A method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity, said method comprising…[administration of taxol].

Nevertheless, the Federal Circuit ***still*** refused to interpret these claims as requiring safety (reducing hematologic toxicity) or efficacy (having antineoplastic results or effecting tumor regression) because "[t]he … method [is] performed in the same way regardless whether or not" hematologic toxicity is actually reduced, the taxol is actually effective in treating the cancer, or the tumor actually regresses. *Id.* at 1277–78; *See also, Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136-1137 (Fed. Cir. 2006) (where the claim called recited "controlled release" the court declined to require "efficacy" even though the only surprising result asserted in support of patentability was effective pain relief in 90% of patients).

MedPointe's intent to misdirect this Court is quite clear, as the same unjustified interpretation is provided for another term at issue, "a medicament", discussed further below. Here, the claims simply do not say that the claimed method and the salt form of azelastine used for such method *must be* safe, effective, or tolerable- desirable as this might be for a specific commercial product- and the Court should resist MedPointe's efforts to so limit the claims.

D. The Plain And Ordinary Meaning Of "A Medicament"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"a medicament"	A product that includes a medicinal substance that has acceptable safety, efficacy, and tolerability for use in humans.	Claim 1 – Ordinary meaning, which includes but is not limited to a formulation containing excipients, preservatives and/or active ingredients, wherein the active

		ingredients include at least a member selected from the group consisting of azelastine and its physiologically acceptable salts in any concentration and may also include other active ingredients, including steroids, decongestants, mast cell stabilizers and/or any other active ingredient commonly used in connection with treating irritation or disorders of the nose and eye. Claims 2-8 – same as claim 1 except as otherwise qualified in claims 2-8, respectively. Claim 9 – same as claim 1, except the dosage form is further limited to a formulation appropriate for spraying, including but not limited to solutions (including aqueous solutions), suspensions, and powders. Claim 10 – same as claim 1, except the dosage form is further limited to a formulation appropriate for application by dropping, including but not limited to solutions (including aqueous solutions), suspensions, powders, gels or ointments.

The term "medicament" is found repeatedly in the claims, but only once in the specification, at col. 8, line 36. However, throughout the patent specification, the term "formulations" is used to describe compositions containing azelastine that are used in the claimed methods. The medicaments of the claims are, or result from, formulations discussed in

the specification, at least because the components of the medicament enumerated in the claims are discussed in the text of the patent as components of the "the formulations of the invention". (Ex. A, the '194 patent, col. 2:35–36; col. 3:26.) The '194 patent provides numerous examples of medicaments, including at col. 2:14–17, naming "drops, ointments, creams, gels, insufflatable powders … a spray" and col. 3:26–28 plainly says that contemplated formulations include "solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, [and] dosage aerosols." Furthermore, the '194 patent expressly encompasses medicaments having "solid or semi-solid formulations". (Ex. A, the '194 patent, col. 4:11–12.) Several example medicaments and their formulations are provided in Examples 1–4. (Ex. A, the '194 patent, col. 6:6–7:46.)

The file history further supports this understanding of medicament, variously describing the composition containing azelastine according to the claims as a "pharmaceutical preparation" (Ex. B, Prosecution History Excerpts, at MP0092–93). Claim 1 is also described as a method which "comprises *applying* azelastine *directly to the nasal tissues or to the conjunctival sac of the eye*" (emphasis in original) and that "[c]laims 2-8 relate to more preferred features of the pharmaceutical composition containing azelastine." (Ex. C, Prosecution History Excerpts, at MP0113.)

Because the independent claims 1 and 12 of the '194 patent say a "medicament which *contains*" azelastine or a salt thereof, it is clear that the medicament can contain additional components. The nature of these additional components are in no way limited by the other claims, the patent specification, or the file history, and therefore can include additional active compounds known in the art as well as inactive compounds, some of which are enumerated in the '194 patent. For example, the dependent claims show that the medicament of claim 1 can,

but need not, include a preservative such as benzalkonium chloride or thimerosal (claims 5, 8, discussed further *infra*) and a solvent (claim 6) that may be water (claim 7). The medicament of claim 1 can contain any concentration of azelastine, because the scope of claim 1 must be broader than that of dependent claims 2-4 specifying particular concentrations. *See Philips,* 415 F.3d at 1314–15 (there is a presumption that limitations added in a dependent claim is absent from the independent claim).

Furthermore, the nature of open transitional terms like "contains" and "comprises" means that additional components or steps can be present even if not named or even considered by the inventor. *E.g.*, *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1371 (Fed. Cir. 2005) ("The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended."); *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382 (Fed. Cir. 2000) ("The phrase 'consisting of' is a term of art in patent law signifying restriction and exclusion, while, in contrast, the term 'comprising' indicates an open-ended construction."); *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("containing", "comprising", and "including" are synonymous and mean that the claim does not exclude additional components or steps). Accordingly, the medicament of the '194 patent claims can even include other active ingredients as this limitation is simply absent from the claims.

Notably, the record before us shows that "medicament," like "physiologically acceptable," does not denote a preparation necessarily having "acceptable safety, efficacy, and tolerability for use in humans" when applied directly to the eyes or nose[3]. As noted *supra*, one will search the specification for the word "safe" or "safety" without success, and find "tolerated"

[3] MedPointe's position also suggests that if a medicament containing azelastine is used in a veterinary setting or is found to be intolerable by any patient when applied to the eye or nose, then such a use would be outside the claims.

exactly once. Similarly, the patent does not use the word "human" or even "person". The only reference to a human is indirect, in that one might assume the trial subjects (Ex. A, the '194 patent, col. 1:63–64), may have been human. Importing the limitation that the medicament is for use on humans (only) is merely a strategy to escape invalidating prior art describing *inter alia* topical administration of azelastine to non-human animals to treat allergic reactions. (Ex. D, Chand *et al.*, 58 ANN. ALLERGY 344-49 (1987).)

Apotex believes the term "medicament" should be given its ordinary and customary meaning, and that such meaning is a medicinal substance or preparation having (in, e.g., any of the forms listed in the patent) that is used or intended to treat the symptoms or cause of a disease or ailment. Efforts by MedPointe to limit the claims to treatments where the medicament has "acceptable safety, efficacy, and tolerability for use in humans" should be rejected as these new limitations lack any support in the record.

E. The Plain And Ordinary Meaning Of "The Medicament Contains 0.003 To 0.5% (Weight/Weight) Of Azelastine Or An Amount Of A Physiologically Acceptable Salt Of Azelastine Which Contains 0.003 To 0.5% (Weight/Weight) Azelastine"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine"	The medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine in which the weight of azelastine base is 0.003 to 0.5% of the weight of the medicament. Includes a 0.0033 to 0.55% (weight/volume) aqueous solution of azelastine hydrochloride.	Includes salts of azelastine in which the weight of azelastine base is 0.003 to 0.5% of the weight of the medicament.

Apotex contends that "the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine" simply means that the medicament includes salts of azelastine in which the weight of azelastine base is 0.003 to 0.5% of the weight of the medicament.

F. The Plain And Ordinary Meaning Of "Aqueous Solution"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"aqueous solution"	Ordinary meaning.	Ordinary meaning, which includes a formulation wherein the excipients, preservatives, and/or active ingredients are dissolved in a solvent and the solvent is water.

Apotex contends "aqueous solution" should be accorded its ordinary meaning, which means that the medicament has a formulation wherein the excipients, preservatives, and/or active ingredients are dissolved in a solvent and a solvent is water. As noted above, other solvents are expressly named as preferred solvents for the medicament described in the '194 patent. See e.g., col. 2 lines 35-45, naming water, alcohols, and polyglycols as preferred solvents. The specification also says that water can be mixed with the other enumerated solvents to form an "aqueous mixture". (Ex. A, the '194 patent, col. 2:45.) Dissolution of azelastine in such an "aqueous mixture" would still be an aqueous solution even if the mixture contains such additional solvents because the solution also contains water as a solvent.

G. The Plain And Ordinary Meaning Of "Solution Which Contains"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"solution which contains"	Ordinary meaning.	Ordinary meaning, which includes a formulation for direct application to the nasal tissues, wherein any excipients, a preservative and active ingredients are dissolved in a solvent and the preservative is either sodium-2-(ethylmercurithio)-benzoate or akylbenzyldimethyl ammonium chloride in the stated concentrations.

Claim 8 recites that the medicament of claim 1 is "a solution which contains 0.001 to 0.05% weight/volume of solution of sodium -2-(ethylmer-curithio)-benzoate or 0.001% to 0.1% (weight/volume of solution) of alkylbenzyldimethylammonium chloride." Apotex and MedPointe agree that the compounds recited in claim 8 are the preservative compounds commonly referred to as thimerosal (Ex. A, the '194 patent, col. 2:55) and benzalkonium chloride (Ex. A, the '194 patent, col. 3:4.).

Disputed, however, is the simpler term "solution which contains". Apotex contends that this term should be construed to mean the medicament of claim 1 wherein any excipients, a preservative and active ingredients are dissolved in a solvent and the preservative is either thimerosal or benzalkonium in the stated concentrations. As discussed *supra*, the preferred solvents taught to be suitable for the medicament include alcohols, polyglycols, and/or water. It bears repeating that there is no good reason in law or fact to understand a medicament according to the claims to be necessarily safe, effective, or tolerable for use by humans.

H. The Plain And Ordinary Meaning Of "Applied By Spraying"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"applied by spraying"	Delivering a fixed volume (typically, 50 to 150 microliters) of an aqueous solution to nasal tissues by aerosolizing that solution into a fine mist (typically with the size of most droplets falling in the range of 10 to 250 micrometers) targeted to those tissues. Excludes application to the eye and excludes application of drops to the nose.	Ordinary meaning, including but not limited to a method of applying a formulation appropriate for spraying, including but not limited to solutions (including aqueous solutions), suspensions and powders, wherein the formulation spray delivers, for example, drops (solutions, aqueous solutions), streams (solutions, aqueous solutions, suspensions), or particles (powders, suspensions) directly to the nasal tissues or conjunctival sac of the eyes.

Like the claim terms above, MedPointe would have the Court interpret the "applied by spraying" element in claim 9 in a manner that is unjustifiably narrow and contradicts the record. MedPointe would have this Court limit "applied by spraying" to

1) delivering a fixed volume of an aqueous solution containing azelastine,

2) by aerosolizing the aqueous solution, where

3) the resulting drops have a particular size,

4) the drops are targeted to nasal tissues,

5) but excludes application of drops of such a solution to the nose and

6) excludes application to the eye.

See Exhibit B, Joint Claim Construction. None of these limitations comport with the descriptions actually provided by the inventor, and so they lack even the superficial legitimacy attributed to limitations improperly imported from the specification.

Spraying is described as a mode of application for aerosols of suspensions, non-aqueous solutions, and for powders in the specification (Ex. A, the '194 patent, col. 5:17–68) describing various systems by which azelastine can be aerosolized and sprayed into, *e.g.*, the nose; lines 41-42 specifically say aerosolized suspensions are sprayed; example 3 provides an example of a non-aqueous solution or suspension aerosolized and delivered by a device including a pressurized propellant). That spraying of a solution results in drops of a solution is also described. (Ex. A, the '194 patent, col. 5:36–38.) Clearly, these are still *drops* that are applied to nasal tissues. Contrary to MedPointe's proposed construction, no fixed solution volume or drop size is required by the claims, the specification or the file history- all that are provided are the particle sizes for solid particles in suspensions or an insufflatable powder[4]. (Ex. A, the '194 patent, col. 5:48–53.)

With regard to MedPointe's proposed limitation that sprays exclude application to the eyes, the problems are exactly the same as plague MedPointe's other proposed constructions throughout- the specification describes the alleged invention in terms that do not permit such limitations. The specification (Ex. A, the '194 patent, col. 2:14–17) expressly states that "one or more of [azelastine's] salts can be used in the form of … a spray (preferably a nasal spray)." The inventor here ***expressly*** admits of a spray appropriate for and useful in the claimed method that is *not* a nasal spray, even if such a spray is not the preferred embodiment. Since the claims are directed to applying a medicament directly to nasal tissues or to the conjunctival sac of the eye, all that is left is a spray for the eyes. Furthermore, the only difference between claim 1 and

[4]Apotex notes that the specification does not expressly say that aqueous azelastine solutions are applied by spraying into the nose, but Apotex does not assert that such a method would be outside the scope of claim 9.

claim 9 is "applied by spraying": the only new limitation is the act of "spraying", not the site of application.

Accordingly, in claim 9 the spray of a solution are "drops", the volume and drop size are not limited, and sprays are not limited to aqueous solutions or to the nose. Apotex contends, based on the inventor's description of his alleged invention in the specification that "applied by spraying" refers to a method of applying a formulation including azelastine, including but not limited to solutions (including aqueous solutions), suspensions and powders, wherein the formulation spray delivers, for example, drops (solutions, aqueous solutions), streams (solutions, aqueous solutions, suspensions), or particles (powders, suspensions) directly to the nasal tissues or conjunctival sac of the eyes.

I. The Plain And Ordinary Meaning Of "Allergy-Related . . . Symptoms" And "Vasomotor Or Rhino-Related Colds Or Symptoms"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"allergy-related . . . symptoms"	Symptoms of rhinitis due to an IgE-mediated allergen response, including seasonal allergic rhinitis, such as rhinorrhea, nasal congestion, sneezing, and itching of the eyes and nose.	Ordinary meaning, which includes, for example, symptoms commonly associated with seasonal allergic rhinitis (i.e., hay fever).
"vasomotor or rhino-related colds or symptoms"	Symptoms of nonimmunologic, noninfectious, chronic rhinitis such as chronic nasal congestion, rhinorrhea, and sneezing.	Ordinary meaning, which includes but is not limited to vasomotor rhinitis (also known as rhinitis vasomotorica) and colds and symptoms associated with rhinoviral infection.

Apotex contends that "allergy-related . . . symptoms" and "vasomotor or rhino-related colds or symptoms" need not be interpreted as a limitation of claim 12 because it is a part of the

preamble. As discussed *supra*, preambles to claims are non-limiting where the body of the claim sets out the complete invention in that the steps and materials necessary to perform the claimed method are provided in the body of the claim. See e.g., *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1373-4 (Fed. Cir. 2001); c.f. *Eaton Corp. v. Rockwell Int'l Corp.* 323 F.3d 1332, 1339-40 (Fed. Cir. 2003); *Jansen v. Rexall Sundown* 342 F.3d 1329. Here, like in *Bristol-Myers*, the preamble at most sets out desired objectives and results of the claimed method, was not added by amendment to overcome prior art, and does not enumerate necessary structures or antecedents.

Furthermore, as discussed for claim 1 *supra*, if MedPointe contends that the preamble of claim 12 limits the scope of that claim, the preamble is nevertheless subject to the usual methodology of claim construction. Apotex notes that the full preamble of claim 12 is nearly duplicated in the '194 patent specification at col. 2 lines 5-8, which reads, "for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms." This passage, read in context, clearly refers back to the full list of symptoms and conditions provided in col. 1 lines 40-43 and lines 49-52.

With the '194 patent specification in mind, it is apparent that "allergy-related, or vasomotor or rhino-related colds and symptoms" therefore include the conditions and symptoms listed in the '194 patent. Therefore, Apotex contends that the preamble of claim 12, if it limits the scope of that claim, must include at least the allergy-related, vasomotor, and rhino-related conditions listed in the '194 patent specification. Such conditions and symptoms include those commonly associated with allergic rhinitis (i.e., hay fever), vasomotor rhinitis (also known as rhinitis vasomotorica) and colds and symptoms associated with rhinoviral infection.

Regarding the term "rhino-related colds or symptoms" in particular, Apotex contends that this term would be understood in the context of the claims, the specification, and the file history to denote infectious conditions and their symptoms such as "the normal common cold (caused, for example, by rhino viruses)," (Ex. A, the '194 patent, col. 1:41–42), and *not* "nonimmunologic, noninfectious, chronic rhinitis" as proposed by MedPointe. The word "rhino" occurs exactly twice in the specification, (Ex. A, the '194 patent, cols. 1:41–2:7). Both times it is used to refer to the infectious agent "rhino virus" and the symptoms caused by it.

J. The Plain And Ordinary Meaning Of "Applying Directly To The Patient's Nasal Tissues Or To The Conjunctival Sac Of The Patient's Eye"

CLAIM TERM OR PHRASE	MEDPOINTE'S PROPOSED CONSTRUCTION	APOTEX'S PROPOSED CONSTRUCTION
"applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye"	Topical application to the nose or to the conjunctival sac of the eye. Excludes oral and parenteral applications.	Ordinary meaning, including but not limited to application directly to mucous membranes of the nose and eye.

The phrase "applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye" should be given its ordinary and accustomed meaning. The parties do not really dispute what the meaning of technical terms like "conjunctival sac". The issue of whether a particular accused infringing use or a particular prior art reference meets the limitation of "applying directly" poses a question of fact. It would be inappropriate to resolve these factual questions involving comparison of the claim to accused infringements and/or to prior art by a purported "claim construction" that does not say what the claim terminology is, but instead what it is not.

CONCLUSION

For the reasons set forth herein, Apotex respectfully requests that the disputed claim terms be accorded their plain and ordinary meaning, without importing extraneous limitations either from the specification or especially from extrinsic evidence concerning the process and requirements for FDA approval.

Respectfully submitted,

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Dated: December 17, 2007
838211 / 30136

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

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EXHIBIT A

US005164194A

United States Patent [19]

Hettche

[11] **Patent Number: 5,164,194**

[45] **Date of Patent: Nov. 17, 1992**

[54] **AZELASTINE CONTAINING MEDICAMENTS**

[75] Inventor: **Helmut Hettche**, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: **Asta Pharma AG**, Fed. Rep. of Germany

[21] Appl. No.: **551,644**

[22] Filed: **Jul. 12, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, abandoned.

[30] **Foreign Application Priority Data**

Nov. 13, 1987 [DE] Fed. Rep. of Germany 3738681

[51] **Int. Cl.**[5] **A61K 9/14**; A61K 31/55

[52] **U.S. Cl.** **424/489**; 424/43; 424/45; 424/464; 424/422; 514/212

[58] **Field of Search** 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

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[57] **ABSTRACT**

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

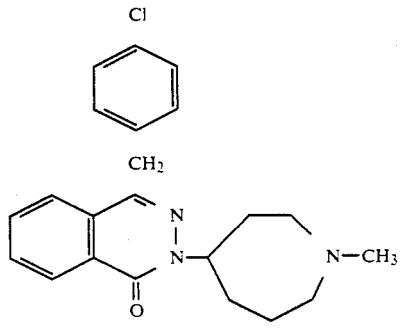
AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No. 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

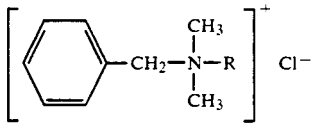
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preserva-

tives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present-as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, **68** g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium.

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, $D.^{25}$ ca. 1.1, F. 40°–44° C. Solidification point ca. 41° C.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26–88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim **1** in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim **2** in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim **1** in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim **1** in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim **1** in which the medicament is a solution.

7. A method as set forth in claim **1** in which the medicament is an aqueous solution.

8. A method as set forth in claim **1** in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim **1** in which the medicament is applied by spraying.

10. A method as set forth in claim **1** in which the medicament is applied as drops.

11. A method as set forth in claim **1** in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO.	:	5,164,194
ISSUED	:	November 17, 1992
INVENTOR(S)	:	Helmut Hettche
PATENT OWNER	:	Asta Medica, AG

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

349 days

from November 17, 2009, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of February 1998.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and

EXHIBIT B

12/B

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of

Helmut HETTCHE

Serial No. 07/551,644 Group Art Unit: 152

Filed: July 12, 1990 Examiner: L. Piccone

For: AZELASTINE-CONTAINING MEDICAMENTS

June 17, 1991

6-27-91
Linda B.

* * * * *

RECEIVED
JUN 24 1991
GROUP 150

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

Responsive to the Office Action dated January 25, 1991, please amend the above-identified application as follows:

IN THE CLAIMS:

Rewrite claims 1-4 and 12 as follows:

1. (amended) A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member [of] selected from the group consisting of azelastine and its physiologically acceptable salts.

2. (amended) A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. (amended) A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. (amended) A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

12. (amended) A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member [of] selected from the group consisting of azelastine and its physiologically acceptable salts.

REMARKS

The applicant respectfully requests reconsideration.

The claims have been amended in several respects to deal with the rejections under 35 U.S.C. 112. Thus, for example, the language introducing the Markush groups in claims 1 and 12 has been changed to the form suggested by the Examiner. In claims 2-4, the amounts of the physiologically acceptable salts has been described. This amendment is based on the disclosure on page 5, lines 6-8 from the bottom.

However, applicants submit that the phrase "predetermined amount" in claim 15 is not indefinite. The precise amount which is released when the atomizing container is actuated, of course, depends on two factors. First, it depends on the concentration of azelastine in the liquid in the aerosol container. Secondly, it depends on the amount of liquid which is released when the aerosol container is actuated. The two factors are selected so that the patient receives the dosage which is desired. The word

"predetermined" in this case does not imply any particular amount of liquid. Rather, it indicates that the aerosol container is one which releases a fairly precise amount each time it is actuated, so that the patient receives a desired amount.

In claim 18, it is thought that the conventional pharmaceutical carrier substances are known and need not be defined precisely. In this case, the active ingredient, azelastine, is put up in a powder. The kinds of inert components which are used to produce a pharmaceutical powder are known. While the terminology is broad, it is submitted that it is not indefinite.

Applicants respectfully traverse the rejection of claims 11 and 18 as lacking an enabling disclosure. The specification clearly teaches that it is possible to put up the claimed medicines in pharmaceutical powders. The concentration of active ingredient in the powders is disclosed at page 5, last three lines. The particle size is disclosed at page 10, lines 14-16. It is submitted that this provides sufficient information for a person skilled in the art to make the claimed compositions in the form of powders.

Applicant respectfully requests reconsideration of the rejection of claims 1, 6, 7, 9, 10, 11 and 12 as anticipated under 35 U.S.C. 102 over Vogelsang. These claims recite that azelastine is applied "directly to nasal tissues or to the conjunctival sac of the eye", and this process step is not disclosed in Vogelsang.

In discussing this ground of rejection on page 3 of the Office Action, the Examiner has not cited any portion of the reference which teaches this step. The comment that Vogelsang discloses the use of azelastine in a pharmaceutical

preparation that can be administered in usual embodiments such as tablets, etc. does not support an assertion that the reference discloses the specific form of administration claimed in this application, within the context of 35 U.S.C. 102. That provision of the patent statute is quite specific in requiring that the reference actually disclose the process which is claimed. A similar comment can be made with regard to the Examiner's contention that aerosol administration is disclosed in the reference, with the further comment that the reference does not disclose aerosol administration of azelastine (see discussion below).

The following are some of the legal authorities which define the scope of 35 U.S.C. 102.

> Ex parte Meyer, 213 USPQ 588, 590
>
> To anticipate a claimed invention, all limitations in the claims must be found in the reference since the claims measure the invention....Moreover, a rejection under 35 U.S.C. 102(e) necessarily implies that the invention is not new, i.e., that there is no difference between what is claimed and what is disclosed in the prior art. (Emphasis added.)
>
> Ex parte Stubbs, 149 USPQ 641
>
> Claims 7 and 8 are rejected as unpatentable over Jones et al. It is stated in the answer that this rejection is under 35 USC 102. However, it is apparent from the Examiner's position as to these claims that the rejection can only be under 35 U.S.C. 103 because the claims include a limitation that is not shown in the reference.
>
> In re Kalm, 154 USPQ 10
>
> A rejection under 35 U.S.C. 102(e)...necessarily implies that the invention sought to be patented has been described...that there are no differences between what is claimed and what is disclosed....

The reference simply does not disclose the step of administering azelastine "directly to nasal tissues or to the

conjunctival sac of the eye". Therefore, this ground of rejection is thought to be inappropriate.

Applicant also requests reconsideration of the rejection of the claims under 35 U.S.C. 103. Contrary to the Examiner's contention, it is submitted that Vogelsang does not disclose administering azelastine "directly to nasal tissues or to the conjunctival sac of the eye". The passages cited by the Examiner do not establish the contrary.

Column 1, line 57 discloses a category of active ingredients which include azelastine, and, as the Examiner has said, azelastine is specifically exemplified in the patent. However, this particular passage does not say anything about the mode of administration.

Column 6, line 65 which the Examiner has cited discloses various dosage forms, but, again, there is no disclosure of direct administration to nasal or eye tissues. While treatment of disorders of the skin and mucus membranes are mentioned, direct administration to nasal tissues and the conjunctival sac of the eye are not mentioned.

The Examiner has also referred to the disclosure of an aerosol, but applicant submits that the Examiner has misunderstood this disclosure. The reference does not teach putting up azelastine in an aerosol. The aerosol is used to administer histamine in a guinea-pig test. The Examiner has referred to Column 6, line 21 which is the heading for Table I. It refers to Histaminolytical activity in the histamine aerosol test on guinea-pigs. This test is described in Column 5, lines 49-63. In that test, the guinea pigs inhale an aerosol of histamine. The test compounds, such as azelastine, are administered "subcutaneously or orally" (column 5, line 58). Therefore, the disclosure of

aerosols in this reference is wholly unrelated to the use of aerosols in connection with the present invention.

The invention provides numerous advantages associated with other forms of administration. These are discussed on pages 1 and 2 of the present application. The Examiner has pointed to the declarations submitted previously, but of course these are concerned with a comparison with a different reference. These declarations show that azelastine is more effective than other active agents disclosed in the Engel reference which was cited previously. However, since the Vogelsang reference actually discloses azelastine, it raises entirely different issues.

The only routes of administration actually disclosed in Vogelsang are subcutaeous (parenteral) and oral. There is no evidence that azelastine would be effective when applied directly to nasal tissues or to the eye. The advantages of the present invention relate to a different mode of administration, but there is no suggestion of them in this reference. This is reinforced by Examples 43-46 which relate to dosage units, i.e., tablets, dragees, suppositories and injection ampoules.

Finally, applicants request reconsideration of claims 13-17. The Examiner has shown that the various appliances covered by those claims are known and that they have been used to administer medications. There can be no doubt that these appliances are not broadly new as a way to administer medications. However, it is submitted that it would not have been obvious to put up azelastine in these kinds of appliances, because it was not obvious to administer azelastine to parts of the body for which these types of appliances are suited.

For these reasons, it is submitted that the present invention is patentable, and that all informalities in the claims have been corrected. Favorable reconsideration of the claims and allowance are respectfully requested.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

By _____
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Telephone (202) 861-3000

EXHIBIT C

110.00, 15 260.00 + 0.00 64/152

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED
MAY 0 8 1992
GROUP 150

In re PATENT Application of

Helmut HETTCHE

Serial No. 07/551,664 Group Art Unit: 152

Filed: July 12, 1992 Examiner: L. Piccone

For: AZELASTINE-CONTAINING MEDICAMENTS

19/EXT (1) & Brief

April 28, 1992

BRIEF FOR THE APPLICANT

Dell 5/11/92

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This is an appeal from the final rejection of claims 1-12 and 18.

STATUS OF CLAIMS

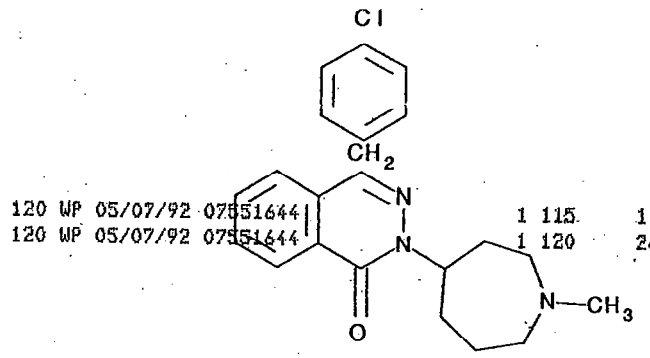
The application originally contained claims 1-18. Claims 13-17 have been cancelled, leaving claims 1-12 and 18, which are presented in this appeal.

STATUS OF AMENDMENTS

An amendment was submitted after the final rejection, cancelling claims 13-17. It has been entered.

SUMMARY OF THE INVENTION

The invention relates to a new use of azelastine, a phthalazinone derivative having the formula:



120 WP 05/07/92 07551644 1 115 110.00 CK
120 WP 05/07/92 07551644 1 120 260.00 CK

Azelastine has been used in prophylactic treatment of asthma and for its anti-allergic and antihistamine properties.

The present invention is based on a surprising discovery that azelastine and its physiologically acceptable salts display advantageous and surprising effects when applied directly in the nose and/or to the conjunctival sac of the eye. This treatment produces elimination or marked relief in allergy-related rhinitis, the common cold, and vasomotor cold. Further, application directly in the nose has been found to have advantageous effects on the mucous membrane of the eye.

The invention is claimed in claim 1 as a method which comprises *applying* azelastine *directly to the nasal tissues or to the conjunctival sac of the eye.* Claims 2-8 relate to more preferred features of the pharmaceutical composition containing azelastine which is applied in accordance with the method of claim 1. Claims 9-11 relate to more preferred modes of application of the azelastine-containing composition. Claim 12 is similar to claim 1, in defining a method of treatment with azelastine. However, it defines the symptoms which are treated more specifically than in claim 1, i.e., "a patient suffering from allergy-related or vasomotor or rhino virus-related colds or symptoms."

Claim 18 relates to a novel composition containing azelastine which is useful for the present invention. More specifically, Claim 18 relates to a powder containing azelastine and an appropriate pharmaceutical solid carrier.

ISSUES

The Examiner has rejected claims 1-12 and 18 as obvious under 35 U.S.C. § 103 over Vogelsang, U.S. Patent 3,813,384 "in view of art admitted in the specification." The Examiner separately rejected claims 13-17. However, since those claims have been cancelled, it is assumed that the

grounds of rejection applied against those claims are no longer at issue.

GROUPING OF CLAIMS

The Examiner has grouped claims 1-12 and 18 together. However, applicants believe that claims 1-12 should be considered separately from claim 18.

ARGUMENT

Claims 1-12 and 18 stand rejected as obvious from the disclosure of the cited Vogelsang, et al. patent in view of "the art admitted in the specification." The claims relate to administration of azelastine directly into nasal and eye tissues.

It is not clear what aspects of the art admitted in the specification is the basis of the examiner's reference, but the introductory passage on page 1 simply mentions to the fact that azelastine has anti-allergic and anti-histamine properties. This information does not imply a mode of administration, although, as shown below, the customary mode of administration for such medications is systemic (e.g., oral or injection). Further, as the cited Vogelsang patent refers to the fact that its compounds are used for the treatment of histamine induced disturbances (see Abstract, Column 1) and allergies (Column 6, line 72), it is not seen where the above cited passage adds anything to the disclosure of the Vogelsang patent. The Examiner has referred on page 3 of the Office Action to the use of "preseruahres" (sic) in this connection, but this comment is not understood. Therefore, it is the disclosure of the Vogelsang patent which is the focus of the following remarks.

In his discussion of this patent, on page 3 of the Final Rejection, the Examiner has referred to column 43 lines 5-15 of Vogelsang, but this comment also is not understood. There is no column 43 in this patent.

The only information in the Vogelsang patent on mode of administration is in the paragraph bridging columns 6 and 7, viz.

> The compounds according to the present invention are used as active ingredients in pharmaceutical preparations and may be administered in *usual embodiments such as tablets, dragees, capsules, suppositories, drops, ointments, creams as well as injection solutions.* They are in particular used for the treatment of the various forms of allergies. Thus, they have been used successfully in humans in the treatment of asthma bronchiale, for the treatment of various disorders of the skin and mucous membranes hay fever and rhinitis vasmotorica. In general, they are administered in such treatments in a dosage of 0.4 to 4 mg. per day and human patient. The symptoms of the above allergic diseases may be effectively reduced upon a single dose for up to 24 hours. The effectiveness of the components of the present invention in humans which is produced very rapidly and over a prolonged period of time in comparison to other antihistamines, may be particularly well-shown in the reduction of the size of an artificially produced lesion by means of a histamine liberator according to L. Kerp, H. Kasimiar, P.N. Tie, Med. Welt 17 NF 2794 (1966). The compounds according to the present invention may be used as such or in combination with other active ingredients as they are usual in antihistaminic preparations.

The portion which has been shown in italics above appears to be the sole basis for the rejection, and more particularly the disclosure that the compounds "may be administered in...drops..." To this, the Examiner has added the following comment:

> It would have been obvious to administer the azelastine composition of Vogelsang directly to the nasal tissues or conjunctival sac...because these are the areas to which medicament drops are normally applied.

However, the Examiner has indulged in a leap of logic which is not supported by the reference in making this comment. The reference does not say that drops are administered to the patient. It merely says that the compounds may be administered in drops. Thus, a medicine dropper is a

well known device for measuring liquids. See for example page 1329 in the attached extract from *The United States Pharmacopoeia* which describes the use of a medicine dropper and its ability to deliver a measured quantity of liquid, with various degrees of precision. But there is no indication of where the drops are to be delivered. For example, a medicine dropper is used as a means of delivering a measured quantity of a concentrated liquid to water which is to be swallowed or used as a mouthwash.

The Examiner has cited no reference to support his contention that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, such a sweeping statement, which provides the sole link between the Vogelsang patent and the present invention, should be supported by a reference.

Referring again to the attached extract from *The United States Pharmacopoeia*, it will be noted that various modes of administration are discussed. Compositions which are intended to be administered to the nose are referred to as "Nasal Solutions" and compounds which are administered to the eye are referred to as "Ophthalmic Solutions", see pages 1655 and 1338. On the other hand, among the forms of medicine which are described, the word "drops" does not appear as a form of material to be administered to the eyes or nasal passages.

Similarly, the words "ointment" and "cremes" are used in the reference, and these are mentioned in the attached copy of an extract from Remington's *Pharmaceutical Sciences*. See pages 1594 and 1616. However, there is no indication of direct application to nasal passages and eyes.

Finally, there is attached a copy of an extract from *Drug Facts and Comparisons*. While numerous antihistamines are mentioned, and modes of administration are described, there is no suggestion of direct application to the eyes and

nasal passages. Dosage forms such as capsules, tablets, injections, suppositories, elixirs and syrups are described, but none for direct application to the eyes and nasal passages.

Therefore, the only link between the present invention and the cited Vogelsang reference is the Examiner's interpretation of the word "drops" in this patent, and the Examiner's unsubstantiated comment that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, as indicated above, such a sweeping statement, providing the sole link between the reference and the present invention and the cited patent, ought to be supported by a reference. Since none has been cited, it is submitted that the claims should be allowed.

Further, applicant requests that the Board consider the decision in the case of *Ex parte Keith*, 154 USPQ 320, which held:

> Asserted inherency must be a necessary result and not merely a possible result. Ex parte Vander Wal et al., 705 O.G. 5, 1956 USPQ 11, 109 USPQ 119, and decisions cited therein.

Here, the Examiner reasons that the only possible meaning of the reference to "drops" in the reference is that they are to be applied directly to the eyes and nasal passages. However, the Examiner has not shown, by citation of a reference, or in any other way, that this is the only possible meaning of the word "drops." Rather, a medicine dropper is simply a device for measuring a liquid. While droppers are used to administer liquid medications to eyes and nasal passages, this does not mean that this mode of administration is the "necessary" and only "possible" inference to be drawn from the reference to "drops" in the cited patent.

The foregoing comments are applicable to both claims 1-12 and claim 18. However, the following additional com-

ments are thought to be appropriate specifically to claim 18.

Claim 18 relates to a powder containing azelastine and a pharmaceutical carrier. Powders are not among the materials mentioned in the cited Vogelsang patent, and so this claim is clearly patentable.

CONCLUSION

For these reasons, it is submitted that the claims are patentable and that they should be allowed.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

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EXHIBIT D

Inhibition of acute lung anaphylaxis by aerosolized azelastine in guinea pigs sensitized by three different procedures

Naresh Chand, DVM, PhD; Kevin Nolan, BA; William Diamantis, PhD; and R. Duane Sofia, PhD

The influence of aerosolized azelastine on acute lung anaphylaxis in actively sensitized guinea pigs (experimental asthma model) was studied. Azelastine administered as an aerosol produced significant inhibition of acute lung anaphylactic responses, ie, the reduction in dynamic lung compliance and an increase in pulmonary airway resistance. These data showed that regardless of the method of sensitization and time of administration (immediately or 15 minutes before antigen challenge), aerosolized azelastine affords significant protection against acute lung anaphylaxis. The inhibition of acute lung anaphylaxis by aerosolized azelastine in the guinea pig asthma model may be due to (1) inhibition of the synthesis/release of chemical mediators, eg, histamine and leukotrienes, etc and/or (2) antagonism of the pharmacologic mediators at the receptor site in respiratory smooth muscles.

INTRODUCTION

Azelastine [4-(*p*-chlorobenzyl)-2-hexahydro-1-methyl-1H-azepine-4-yl)-1-(2H)-phthalazinone hydrochloride] (Fig 1) is a new antiasthmatic/antiallergic drug.[1-12] Azelastine has been reported to inhibit allergic bronchospasm and passive cutaneous anaphylaxis (PCA) in rats and guinea pigs.[1-4] Orally administered azelastine also inhibits leukotriene (SRS-A)-mediated allergic bronchospasms in guinea pigs.[4] The broad spectrum of the pharmacologic activities include the following.[9]

(1) Orally effective antiallergic/antiasthmatic drug
(2) Long-acting
(3) Interferes in the synthesis/release of leukotrienes
(4) Inhibits allergic and nonallergic histamine secretion
(5) Inhibits superoxide radical ($\cdot O_2^-$) generation
(6) Inhibits antihistamine-resistant, leukotriene-mediated allergic bronchospasm in guinea pigs
(7) Inhibits IgE-mediated passive cutaneous anaphylaxis in rats
(8) Inhibits aeroallergen-induced bronchospasm in guinea pigs

From Wallace Laboratories, Division of Carter-Wallace Inc, Cranbury, New Jersey.

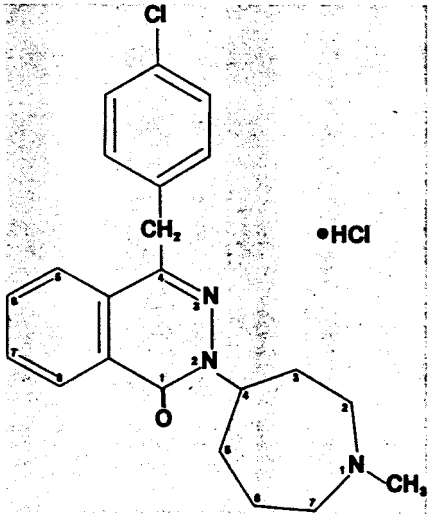

Figure 1. Azelastine [4-(*p*-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepine-4-yl)-1-(2H)-phthalazinone hydrochloride].

(9) Antagonizes pharmacologic mediators at the receptor sites, eg, histamine and leukotrienes

The administration of antiasthmatic drugs via aerosol route offers the following advantages: (1) direct delivery and action of drug at the site of allergic inflammatory responses in the airways and lungs; (2) reduction in doses required to provide strong protection, especially at the time of need, ie, immediately before asthmatic attacks, and (3) increase in the therapeutic index (margin of safety). In the present study, the influence of aerosolized azelastine on acute lung anaphylactic responses ($\downarrow C_{dyn}$ and $\uparrow R_L$) in the guinea pig asthma model was investigated.

MATERIALS AND METHODS

Animals

Adult male Hartley strain guinea pigs (Charles River Breeding Laboratories, North Wilmington, MA) weighing 222 to 539 g were used in this investigation.

Sensitization Procedures

Three different procedures were utilized to sensitize guinea pigs.

(1) Intraperitoneal injection of 1 mg ovalbumin (OA) and 5×10^9 killed *Bordetella pertussis* organisms. These animals were ready for use after 2 weeks.[13]

(2) Intraperitoneal injection of 10 μg OA mixed in 100 mg aluminum hydroxide, $Al(OH)_3$. This procedure of sensitization also produced IgE antibodies.[14] To a 10-mL volumetric flask, add 2000 mg $Al(OH)_3$, 9 mL saline solution, and 1 mL of OA solution (200 μg/mL) and mix the suspension gently. This antigen-adjuvant suspension is prepared one hour before IP injection of 0.5 mL into each guinea pig. These animals were ready for use after 14 days.[14]

(3) Aerosol Sensitization. Eight to ten adult male Hartley strain guinea pigs (200 to 250 g) were placed in an airtight and sealed plexiglass box (40 × 25 × 25 cm) and exposed to ovalbumin aerosol.

Ovalbumin (OA) solution was aerosolized by a Monaghan Model 670 Ultrasonic Nebulizer to produce a fine mist consisting of droplets of 1 to 8 μ in diameter (average diameter of the aerosol particles was about 3 μ). The aerosol sensitization procedure was originally described by Bottomley and his associates.[15] They utilized a thin layer chromatography (TLC) spray gun for aerosolization of OA solution (droplet size varied between 25 to 50 μ, and each guinea pig received about 5 mL over a period of 30 minutes). In the present study, the TLC spray gun was replaced by an Ultrasonic Nebulizer, and duration of aerosol exposure was dependent on the time taken for aerosolization of 100-mL OA solution.

On the first day of sensitization, eight to ten guinea pigs were exposed to 100 mL of OA solution (1%, ie, 10 mg/mL) aerosolized at a rate that gave a constant fine mist for about 90 to 105 minutes. (On day 1, some animals also received an IP injection of 2.2×10^{10} killed *Bordetella pertussis* organisms to enhance sensitization.) On day 5, guinea pigs were exposed to the aerosol of 100 mL OA solution (0.1%, ie, 1 mg/mL) for a period of 60 to 90 minutes. On day 19, guinea pigs were again exposed to an aerosol of 100 mL OA solution (0.001%, ie, 10 μg/mL) for a period of 45 to 60 minutes. Guinea pigs were challenged on days 39 to 43 of sensitization.

The aerosol-sensitization procedure has been briefly summarized in Table 1.

Evaluation of Pulmonary Mechanics (Buxco Pulmonary Mechanics Computer)

On appropriate days of sensitization, guinea pigs were anesthetized with pentobarbital sodium (40 to 50 mg/kg, IP). The jugular vein was cannulated for the administration of succinylcholine. The trachea was exposed and cannulated using an L-shaped tracheal cannula for artificial ventilation. The anesthetized guinea pig was placed in whole body plethysmograph[16] which was connected to differential pressure and flow transducers. One side (+) of the differential pressure transducer was connected to a side arm off the tracheal cannula and the other side (−) was connected to the pleural cavity via a 16-gauge hypodermic needle inserted through the fifth or sixth intercostal space near the sternum. The plethysmograph was sealed off on both sides. The existence of 6-mesh screens in the middle top section of plethysmograph box prevented the pressure build-up and temperature elevation in the box and still allowed the flow measurements. The differential pressure transducer measured transpulmonary pressure. Air flow was measured with a Validyne differential flow transducer attached to the plethysmograph.

The guinea pigs were ventilated with a Harvard small animal respirator set at a stroke volume of 1.5 to 2.5 mL with a frequency of 60 breaths per minute. Each guinea pig was allowed to stabilize for five minutes before spontaneous breathing was arrested with succinylcholine (1.2 mg/kg; procedures #1 and #2) injected IV seven minutes before antigen challenge.[17] The dose of suc-

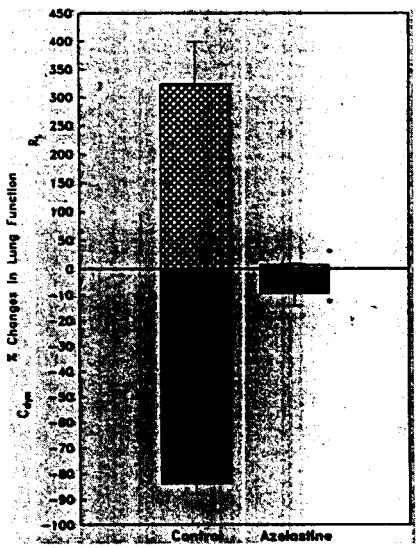

Figure 2. Inhibition of acute lung anaphylaxis by aerosolized azelastine (10 mg/mL, 100 inhalations) administered 15 minutes before antigen challenge (ovalbumin = 0.6 mg/kg IV). Values are means ± SEM (n = 4). *P < .05 as compared to percent increase in pulmonary resistance (%↑R_L) and percent decline in dynamic lung compliance (%↓C_{dyn}) in control 'untreated' guinea pigs (sensitization: procedure 1).

Table 1. Guinea Pig Aerosol Sensitization

	Day	Ovalbumin Solution, 100 mL Monaghan Model 670 Ultrasonic Nebulizer Aerosolization	Duration of Aerosol Sensitization, min
Plexiglass Box (40 × 25 × 25 cm) 8–10 Guinea Pigs Aerosol Particle Size 1–8 μ ≈3 μ	1	1%, 10 mg/mL	90–105
	5	0.1%, 1 mg/mL	60–90
	19	0.001%, 10 μg/mL	45–60
IV Challenge	39–43	Peripheral airway constriction, ↓C_{dyn}	Central airway constriction, ↑R_L

cinylcholine in aerosol-sensitized (procedure #3) animals was 2.5 mg/kg, IV. The electrical integration of the flow signal provided a recording of tidal volume. Lung resistance (R_L = cm H_2O/mL/s) and dynamic lung compliance (C_{dyn} = mL/cm H_2O) were calculated from the transpulmonary pressure, respiratory flow and tidal volume, mathematically integrated by an on-line Buxco Model 6 Pulmonary Mechanics Computer and Data Logger DL 12 utilizing the basic principles described by Amdur and Mead.[18] The Buxco Pulmonary Mechanics Computer was calibrated before each experiment.

Fresh OA solution (100 mg/mL) in saline containing 2% antifoam emulsion (4.9 mL saline + 0.1 mL of antifoam emulsion + 500 mg OA) was made for aeroallergen challenge. The OA solution in drug vials was warmed at 37 °C for at least 30 minutes before antigen challenge. Antigen challenge was continued for a period of 120 seconds (120 breaths). In initial experiments, it was established that the time taken for aerosol delivered from drug vials to the tracheal cannula was 20 seconds. Actual aeroallergen challenge as well as drug administration was therefore given for 100 breaths.

Drugs for aerosol administration were dissolved in glass distilled water and were aerosolized (nebulized) by Monaghan Model 670 Ultrasonic Nebulizer. The size of the nebulized solution varied between 1 to 8 μ in diameter ($\cong$3 μ average aerosol droplet diameter).

Drug aerosol was administered either 15 minutes before or immediately before IV or aerosol antigen challenge. In additional experiments, drug aerosol was also administered simultaneously with antigen aerosol. The control animals always received an aerosol of distilled water as a vehicle.

The percent inhibition of acute lung anaphylactic responses was determined by the following formula:

$$\% \text{ Inhibition} = \frac{A - B}{A} \times 100$$

A = control anaphylactic response (% reduction in C_{dyn}; % increase in

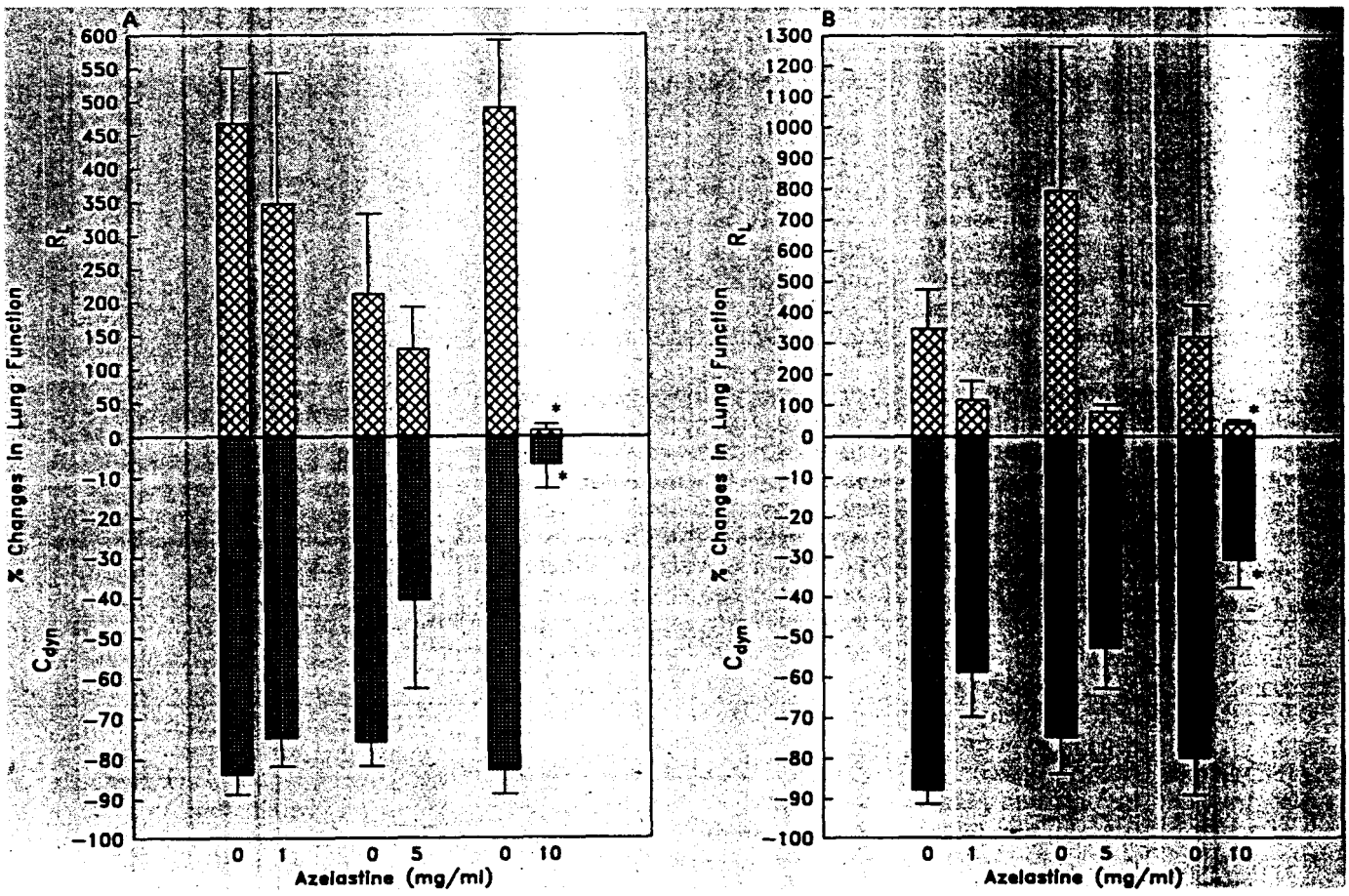

Figure 3. Effect of aerosolized azelastine (1.5 and 10 mg/mL) administered immediately before (A) and 15 minutes (B) before antigen challenge (ovalbumin = 0.3 mg/kg, IV) in guinea pigs. Values are means ± SEM (n = 4–6). *$P < .05$ as compared to percent increase in pulmonary resistance (%↑R_L) and percent decline in dynamic lung compliance (%↓C_{dyn}) in the control 'untreated' guinea pig (sensitization: procedure 2).

R_L) in vehicle-treated guinea pig (one to two guinea pigs each day) and B = anaphylactic responses (% reduction in C_{dyn}; % increase in R_L) in drug-treated individual guinea pig.

The significance of inhibitory activity (mean ± SEM) of azelastine and albuterol was determined by comparing the allergic responses (% change in C_{dyn} and R_L) in drug-treated and untreated vehicle control animals by Student's *t* test for unpaired observations. The statistical significance as implied in this report indicated a *P* value of <.05.

RESULTS

Influence of Aerosolized Azelastine on Acute Lung Anaphylactic Responses Following IV Antigen Challenge

Sensitization Procedure 1: The guinea pigs sensitized with IP injection of OA (1 mg) and *Bordetella pertussis* (5×10^9 killed organisms) responded with 323 ± 76% increase in R_L and 84 ± 4% decline in C_{dyn} upon IV injection of OA (0.6 mg/kg) in aerosol vehicle-treated animals. Azelastine (10 mg/mL, 100 inhalations) administered as an aerosol *15 minutes before antigen* produced statistically significant inhibition of acute lung anaphylactic responses, ie, decline in C_{dyn} and increase in R_L were inhibited by 89% and 97%, respectively (Fig 2).

Sensitization Procedure 2: On days 15 to 18 of sensitization (10 μg OA mixed in 100 mg $Al(OH)_3$, IP) IV injection of OA (0.3 mg/kg) caused a profound decline in C_{dyn} and elevation in R_L in control (distilled water as vehicle aerosol-treated) guinea pigs. Azelastine (1, 5, and 10 mg/mL) administered as an aerosol either immediately or 15 minutes before antigen (OA, 0.3 mg/kg, IV) challenge caused inhibition of allergic responses. The inhibitory effect of aerosolized azelastine on lung anaphylactic responses was statistically significant only at the 10-mg/mL concentration when administered immediately or 15 minutes before antigen challenge (Fig 3a and b).

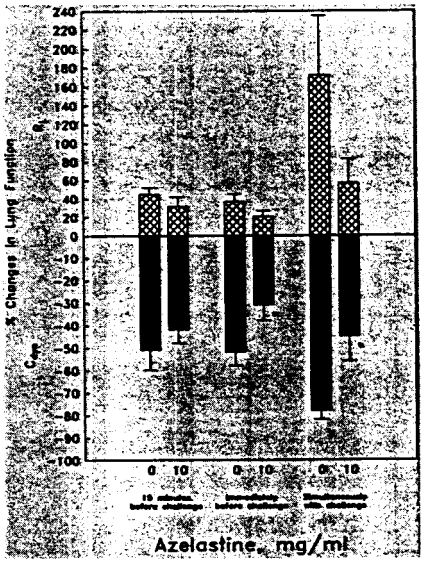

Figure 4. Inhibition of acute lung anaphylaxis by aerosolized azelastine (10 mg/mL, 100 inhalations) administered immediately before, simultaneously, and 15 minutes before aeroallergen challenge (ovalbumin = 100 mg/mL, 100 breaths). Values are means ± SEM. *$P < .05$ as compared to percent increase in pulmonary resistance (%↑R_L) and percent decline in dynamic lung compliance (%↓C_{dyn}) in control 'untreated' guinea pigs (sensitization: procedure 2).

On days 15 to 28 of sensitization, azelastine (10 mg/mL) administered as an aerosol (100 inhalations) immediately before, simultaneously, or 15 minutes before aeroallergen challenge (OA = 100 mg/mL, 100 inhalations) produced 30% to 52% inhibition of acute lung anaphylactic responses (Fig 4, Table 2).

Sensitization Procedure 3 (Aerosol Sensitization)

Aerosol administration of azelastine (10 mg/mL, either immediately or 15 minutes before antigen challenge (OA = 0.6 mg/kg, IV) in aerosol-sensitized guinea pigs produced strong inhibition of decline in C_{dyn} (79% to 92%) and elevation of R_L (90% to 96%) (Fig 5a and b).

DISCUSSION

Azelastine administered as an aerosol exerts inhibitory effects on acute lung anaphylactic responses, ie, decline in peripheral airway constriction and elevation in central airway constriction in the experimental guinea pig asthma model (Table 2). Regardless of the method of sensi-

Table 2. Summary of the Effects of Aerosolized Azelastine in Guinea Pig Asthma Model

Method of Sensitization	Day of Sensitization	Route and Dose of Antigen (Ovalbumin = OA) Challenge	Concentrations of Azelastine 100 Inhalations, mg/mL	Time of Azelastine Aerosol Administration	N	% Inhibition ↓C_{dyn}	% Inhibition ↑R_L
Ovalbumin (1 mg) + *Bordetella pertussis* (5×10^9 cells), IP	14–18	OA, 0.6 mg/kg, IV	10	15 min before	4	89 ± 5.5*	97 ± 0.75*
Ovalbumin (10 μg) + $Al(OH)_3$ (100 mg), IP	15–18	OA, 0.3 mg/kg, IV	1	Immediately before	5	12 ± 6	55 ± 15
			5		5	41 ± 24	52 ± 18
			10		4	39 ± 10*	96 ± 4*
			1	15 min before	5	33 ± 13	53 ± 19
			5		6	29 ± 13	55 ± 18
			10		5	57 ± 15*	71 ± 18*
	15–28	OA, 100 mg/mL, aerosol 100 breaths	10	Immediately before	10	46 ± 12*	52 ± 12
				Simultaneously	7	48 ± 14*	52 ± 16
				15 min before	10	30 ± 8	49 ± 13
Aerosol sensitization	39–43	OA, 0.6 mg/kg, IV	10	Immediately before	3	92 ± 6*	96 ± 2*
			10	15 min before	4	79 ± 16*	90 ± 8*

*$P < .05$ as compared with respective controls.

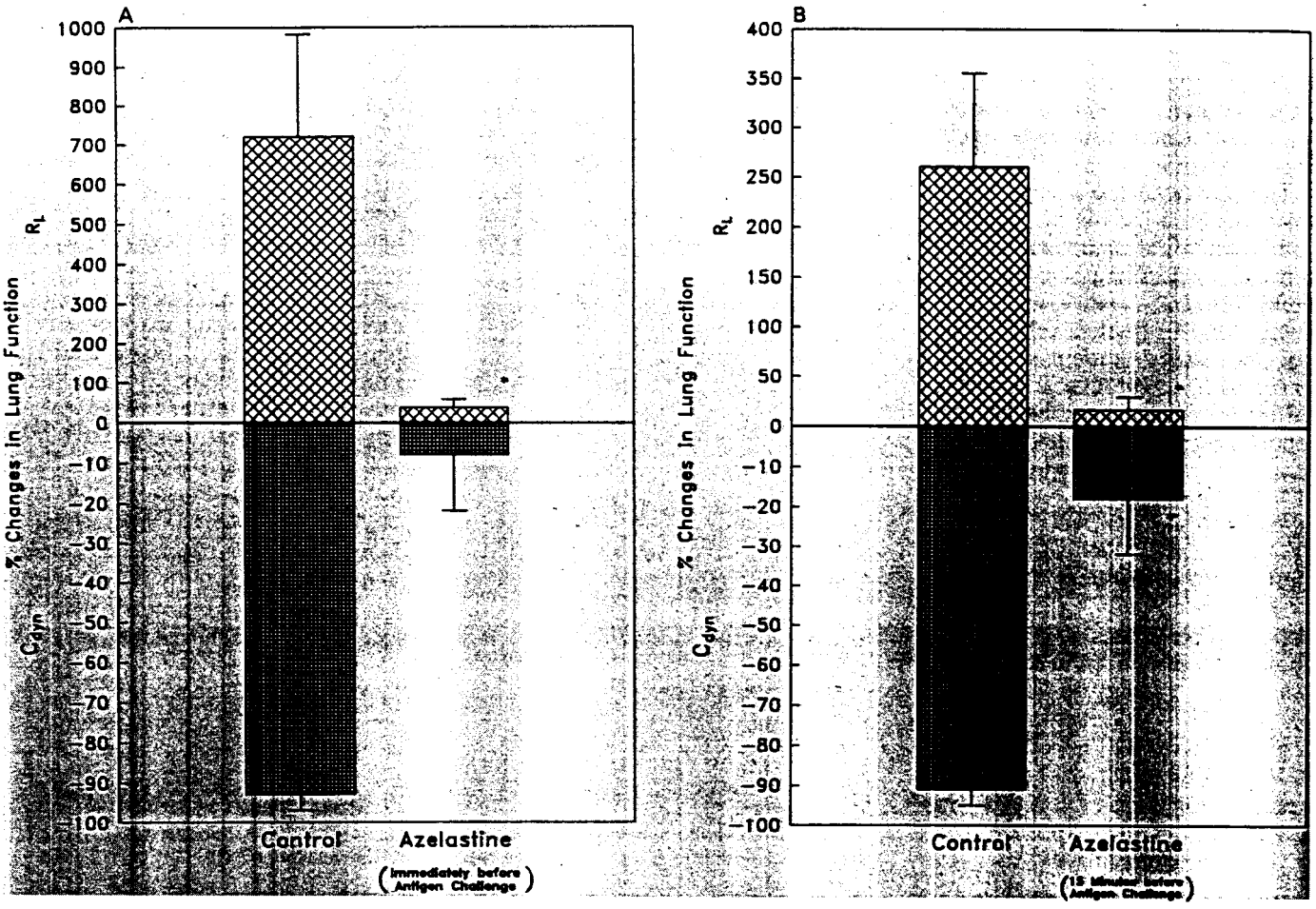

Figure 5. Inhibition of acute lung anaphylaxis by aerosolized azelastine administered immediately (A) or 15 minutes (B) before antigen challenge (ovalbumin = 0.6 mg/kg, IV) in aerosol sensitized guinea pigs (sensitization: procedure 3). Values are means ± SEM. $^*P < .05$ as compared to percent increase in pulmonary resistance (%↑R_L) and percent decline in dynamic lung compliance (%↓C_{dyn}) in the control 'untreated' guinea pigs.

tization (IP or aerosol) and time of administration, aerosolized azelastine (immediately before, simultaneously, and 15 minutes before antigen challenge) administered at a concentration of 10 mg/mL as aerosol for a period of 100 seconds (100 breaths) provided statistically significant protection against acute lung anaphylaxis (Table 2). The approximate dose delivered to the lungs following azelastine aerosol administration (10 mg/mL, 100 breaths) is estimated to be 10 to 50 μg.

The antiasthmatic activity of aerosolized azelastine may be attributed to its known pharmacologic activities: (1) inhibition of synthesis and/or release of chemical mediators, superoxide free radicals

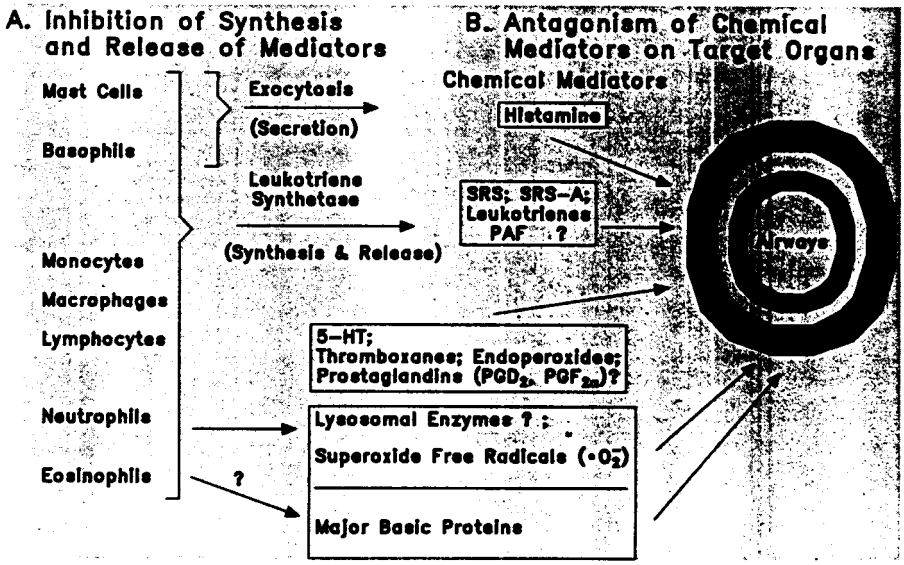

Figure 6. Putative mode of action of azelastine.

($\cdot O_2^-$),[6] histamine, leukotriene C_4 and D_4,[8,9,19-21] (2) antagonism of chemical mediators, eg, histamine and leukotriene C_4 and D_4 (Fig 6),[8,9,22] and (3) possibly the blockade of irritant lung receptors (vagal reflex bronchoconstriction).

Azelastine added to the rabbit leukocytes (basophils) and rat peritoneal mast cells immediately prior (simultaneously) or incubated for ten minutes before secretagogue addition exerts strong, concentration-dependent inhibition of allergic and nonallergic histamine secretion.[8,9,19,20] The *in vitro*[8,9,19,20] and *in vivo* findings in this study demonstrate that azelastine is capable of inhibiting allergic mediator release and subsequent development of bronchoconstriction, even when administered immediately prior to antigen challenge.

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